

# Prospective Study of 288 Episodes of Bacteremia in Neutropenic Cancer Patients in a Single Institution

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Trends in causative organisms and sources of infection were studied in a series of 288 episodes of bacteremia in neutropenic cancer patients observed in a single institution from 1986 to 1993. The incidence of bacteremia increased significantly from 20 episodes per 1000 admissions in 1986 to 50 episodes per 1000 admissions in 1993 ( $p=0.00001$ ). Over the study period, a continuous increment in gram-positive bacteremia, which reached 81% of episodes in 1993 ( $p=0.000001$ ), was observed. Conversely, the incidence of gram-negative bacteremia remained stable. Coagulase-negative staphylococci and viridans group streptococci were the most commonly isolated pathogens. Bacteremia caused by coagulase-negative staphylococci increased from 3 episodes per 1000 admissions to 19 episodes per 1000 admissions ( $p=0.0001$ ), and viridans group streptococci bacteremia increased from 0 episodes per 1000 admissions to 19 episodes per 1000 admissions ( $p=0.000001$ ). The upward trend in gram-positive bacteremia appeared to be related to a significant increase in both intravascular catheters ( $p=0.003$ ) and oral mucositis ( $p=0.003$ ) as sources of infection. Specific strategies to prevent chemotherapy-induced mucositis and catheter-related bacteremia merit further investigations.

Advances in the treatment and supportive care of cancer patients have led to improvement in long-term survival. However, infection remains the most significant complication of therapy (1). Neutropenia, regardless of whether it is induced by therapy or is a consequence of the disease, is the main risk factor for developing a serious infection (2). Bacteremia is the most frequent life-threatening infection in neutropenic cancer patients. It prolongs hospital stay, increases direct patient care costs, and causes considerable mortality despite many advances in antimicrobial therapy (3, 4). Until the late 1970s, gram-negative aerobic organisms were the pathogens most frequently isolated from neutropenic cancer patients (3, 5, 6). In recent years a change in the pattern of pathogens that cause infections in this patient population has been reported, mainly in multicenter clinical trials (4, 7, 8).

We examined 288 episodes of bacteremia in neutropenic cancer patients observed in a single institution over an eight-year period in order to determine the clinical characteristics of these episodes, the sources of infection, and the causative organisms, as well as to evaluate the trends of these variables over time.

## Patients and Methods

*Setting and Source of Data.* The study was carried out in a 1000-bed university teaching hospital in Barcelona, Spain. The hospital serves as a referral center for adults and is located in an urban area with a population of approximately one million. Patients with cancer undergoing cytoreductive chemotherapy are hospitalized at the hematology and oncology divisions, which consist of two 35-bed inpatient units and six isolation rooms. Since January 1988, prophylactic norfloxacin is given orally (400 mg b.i.d.) to patients with cancer who are neutropenic or who are likely to develop cytotoxic therapy-induced neutropenia lasting more than seven days. No other antibacterial prophylaxis is given. All patients receive nystatin  $2 \times 10^6$  U three times daily as a solution whenever possible. Ceftazidime plus amikacin has been the most commonly used empiric antibiotic therapy for febrile episodes over the study period.

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**Table 1:** Characteristics of neutropenic cancer patients in whom 288 episodes of bacteremia occurred.

Characteristic		
Mean age (range) in years	49	(16–87)
Males	176	(61%)
Females	112	(39%)
Underlying disease		
Hematological malignancy	244	(85%)
Acute leukemia	150	
Lymphoma	53	
Other	41	
Solid tumors	44	(15%)
Status of underlying disease		
Determined at diagnosis	32	(11%)
Determined during treatment	256	(89%)

A prospective surveillance of all cases of bacteremia is regularly performed at our institution. All neutropenic cancer patients with bacteremia identified daily by our microbiology laboratory are visited by an infectious diseases physician who fills out a computer-assisted protocol and provides medical advice when indicated. For the purposes of the current study, we examined data from all episodes of bacteremia documented from January 1986 to December 1993.

**Definitions.** Bacteremia (clinical symptoms and positive blood cultures) was considered to be nosocomially acquired if it appeared 48 h after admission and no evidence of infection was present on admission. Neutropenia was considered moderate when the granulocyte count was between  $0.1 \times 10^9/\text{ml}$  and  $0.5 \times 10^9/\text{ml}$ , and severe when less than  $0.1 \times 10^9/\text{ml}$ . Shock was defined as systolic blood pressure  $< 90 \text{ mmHg}$  with signs of peripheral hypoperfusion. Prophylactic antibacterial treatment was considered to be present when norfloxacin was administered for at least three days before bacteremia. Recent antibiotic therapy was defined as administration of parenteral antibiotics for more than 48 h within the two-week period before bacteremia. The source of bacteremia was defined according to previously published criteria (9). Severe mucositis was defined as the presence of multiple ulcerations covering more than 25% of the oral mucosa requiring analgesia with morphine. Overall mortality was defined as death within 30 days of bacteremia. Attributable mortality was defined as death during symptomatic infection or as a consequence of its complications.

**Table 2:** General characteristics associated with 288 episodes of bacteremia.

Characteristic	No. of episodes (%)
Fever	278 (97)
Nosocomial acquisition	216 (75)
Severe neutropenia	209 (73)
Central venous catheter	147 (51)
Prophylaxis with norfloxacin	119 (41)
Previous antibiotic therapy	90 (31)
Severe mucositis	70 (24)
Shock	24 (8)
Septic metastases	13 (5)

**Microbiological Studies.** Between 1986 and 1989, blood cultures were performed using the Roche Septicheck System (Hoffmann-La Roche, Germany) with tryptic soy and thio-glycolate broth media for aerobic and anaerobic cultures, respectively. Beginning in 1990, blood samples were inoculated into Bactec bottles and tested on a Bactec NR-860 instrument (Johnson Laboratories, USA), which detects carbon dioxide by infrared analysis. The bottles were incubated for seven days at  $35^\circ\text{C}$  before being discharged. Bacteria were identified using standard methods (10).

**Statistical Analysis.** Annual incidence rates of bacteremia were computed for neutropenic cancer patients, using the number of admissions to the hematology and oncology divisions as the denominator. Yearly incidence rates were compared using the chi-square test for trends. To compare categorical variables the chi-square test was used. A  $p$  value of  $< 0.05$  was considered statistically significant.

## Results

**General Characteristics of the Episodes of Bacteremia.** During the study period 288 episodes of bacteremia involving 221 neutropenic cancer patients were observed. Forty-two patients had two or more episodes of bacteremia. Sixty-one percent of episodes occurred in males and 39% in females, with a mean age of 49 years (range 16–87). The underlying diseases and disease status are shown in Table 1. Fifty-two percent of episodes occurred in patients with acute leukemia and 8% in patients undergoing bone marrow transplantation. Table 2 shows the main characteristics of the patients in whom bacteremia occurred. During the study period the proportion of nosocomially acquired versus community-acquired cases of bacteremia remained constant.

**Causative Organisms and Sources of Infection.** Table 3 shows the causative pathogens of the episodes of bacteremia according to the sources of infection. A total of 321 organisms were isolated in the 288 bacteremic episodes. Overall, 162 episodes (56%) were caused by gram-positive organisms and 100 episodes (35%) by gram-negative organisms. Twenty-five episodes (9%) were polymicrobial.

The most frequently isolated organisms were coagulase-negative staphylococci (25%), viridans group streptococci (17%), *Escherichia coli* (16%), and *Pseudomonas aeruginosa* (13%). The species of viridans streptococci isolated were *Streptococcus mitis* ( $n = 43$ ), *Streptococcus salivarius* ( $n = 6$ ), *Streptococcus sanguis* ( $n = 2$ ), and *Streptococcus anginosus* ( $n = 2$ ). The source of infection was identified in half of the episodes.

The most frequent sites of infection were indwelling venous catheters (17%), the oral mucosa

**Table 3:** Organisms isolated and sources of infection in 288 episodes of bacteremia.

Organism	Source of infection <sup>a</sup>					Total <sup>b</sup>
	Unknown origin (n = 143)	Catheter (n = 48)	Pneumonia (n = 31)	Mucositis (n = 33)	Other sources (n = 33)	
Gram-positive bacteria	74 (49%)	49 (96%)	19 (51%)	34 (97%)	24 (52%)	200 (62%)
Coagulase-negative staphylococci	29	36	2	3	9	79
Viridans group streptococci	19	0	4	25	5	53
<i>Streptococcus pneumoniae</i>	0	0	11	3	1	15
<i>Staphylococcus aureus</i>	8	6	1	2	4	21
Enterococci	5	3	0	1	5	14
Others	13	4	1	0	0	18
Gram-negative bacteria	78 (51%)	2 (4%)	18 (49%)	0 (0%)	22 (48%)	120 (37%)
<i>Escherichia coli</i>	35	0	5	0	12	52
<i>Pseudomonas aeruginosa</i>	25	2	12	0	4	43
Others	18	0	1	0	6	25
Anaerobes	0 (0%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	1 (1%)
Total	152	51	37	35	46	321

<sup>a</sup> Number in parentheses under each source represents the number of episodes due to that source.

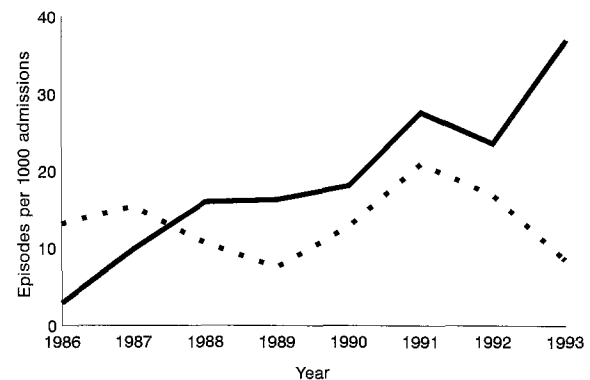
<sup>b</sup> In 25 episodes of bacteremia more than one organism was isolated.

(11%), and the lower respiratory tract (11%). The type of organisms isolated varied, depending on the source of infection. In the episodes of bacteremia of unknown origin, gram-negative bacilli (51%) and gram-positive cocci (49%) were isolated almost equally. In cases of catheter-related bacteremia, the causative pathogens were predominantly gram-positive (96%), mainly coagulase-negative staphylococci (71%). In cases of mucositis, the great majority of isolates were also gram-positive cocci (97%), especially viridans group streptococci (71%). When the source of bacteremia was the lower respiratory tract, gram-positive (51%) and gram-negative (49%) bacteria were isolated equally, with *Pseudomonas aeruginosa* (32%) and *Streptococcus pneumoniae* (30%) being the most frequent causative organisms.

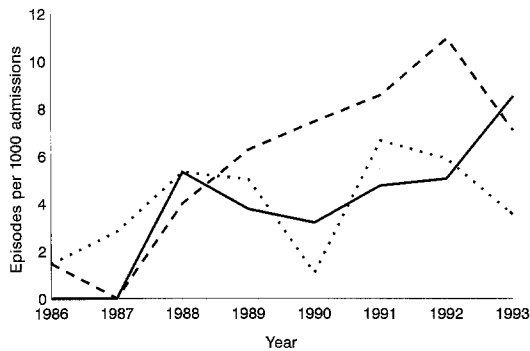
**Trends.** The incidence of bacteremia increased significantly, from 20 episodes per 1000 admissions in 1986 to 50 episodes per 1000 admissions in 1993 ( $p=0.00001$ ). In a year-by-year comparative analysis performed to evaluate the changes in the organisms causing bacteremia, we observed a continuous increase in gram-positive bacteremia, reaching 81% of episodes in 1993 ( $p=0.000001$ ). Conversely, the incidence of gram-negative bacteremia remained stable (Figure 1).

It should be emphasized that the number of episodes of bacteremia per 1000 admissions due to coagulase-negative staphylococci and viridans

group streptococci increased dramatically over the study period; from three to 19 cases ( $p=0.0001$ ) and from 0 to 19 cases ( $p=0.000001$ ), respectively. Enterococcal bacteremia also increased significantly ( $p=0.01$ ), whereas bacteremia due to *Staphylococcus aureus* and that due to *Streptococcus pneumoniae* remained stable. An increase in *Escherichia coli* bacteremia was observed from 1990 to 1993. Bacteremia due to *Pseudomonas aeruginosa* did not decrease during the study period. In fact, bacteremia due to any gram-negative bacilli did not increase significantly over the time period.



**Figure 1:** Trends of gram-positive (solid line) and gram-negative (dotted line) bacteremia during the study period. Increase in incidence of gram-positive bacteremia,  $p < 0.000001$ ; change in incidence of gram-negative bacteremia,  $p=0.97$ .

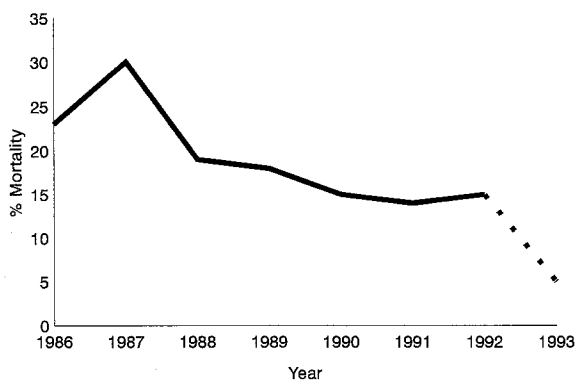


**Figure 2:** Trends in sources of bacteremia over the study period. — mucositis; ..... pneumonia; ---- catheter-related bacteremia. Increase in incidence of bacteremia originating from mucositis,  $p=0.003$ ; change in incidence of bacteremia originating from pneumonia,  $p=0.3$ ; increase in catheter-related bacteremia,  $p=0.003$ .

Regarding the sources of bacteremia (Figure 2), we observed a significant increase in cases of bacteremia in which oral mucositis was considered the origin of infection ( $p=0.003$ ), as well as in cases of catheter-related bacteremia ( $p=0.003$ ).

When we compared trends in the organisms causing bacteremia over time, we did not find significant differences between nosocomial and community-acquired cases. Overall, gram-negative bacteremia was more frequent in community-acquired versus nosocomially acquired episodes: 59% versus 31% ( $p<0.001$ ).

**Outcome.** Overall mortality was 28% and attributable mortality 17%. Thirty-three percent of deaths occurred within 24 h after blood samples for culture were obtained, and 72% of deaths occurred within the first week. Attributable mortality of gram-positive bacteremia was 6%, whereas



**Figure 3:** Trends in mortality over the study period. Decrease in mortality from 1986 to 1992,  $p=0.26$ ; decrease in mortality from 1986 to 1993,  $p=0.005$ .

that of gram-negative bacteremia was 27% ( $p<0.0001$ ). It should be noted that two patients who developed highly penicillin-resistant *Streptococcus mitis* bacteremia and adult respiratory distress syndrome died. During the study period, mortality decreased from 23% in 1986 to 15% in 1992 and to 5% in 1993 ( $p=0.005$ ), as shown in Figure 3. However, if 1993 is excluded from the analysis of trends in mortality, the decrease is not significant ( $p=0.26$ ).

## Discussion

We found an increasing incidence of gram-positive bacteremia among neutropenic cancer patients over the eight-year study period. Coagulase-negative staphylococci and viridans group streptococci were the most commonly isolated pathogens. This finding appears to be related to a significant increase in both catheter infection and chemotherapy-induced mucositis as sources of bacteremia.

This experience concurs with previous studies in which an upward trend in gram-positive bacteremia (4, 6, 8) was found. At the Memorial Sloan-Kettering Cancer Center (New York), gram-positive organisms accounted for 14% of episodes of bacteremia in 1977 and for 23% in 1982 (4). In studies conducted by the International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer, gram-positive cocci, mainly coagulase-negative staphylococci and viridans streptococci, increased in frequency as causative agents of bacteremia, from 29% in the period between 1974 and 1976 (5, 7) to over 65% in the period between 1988 and 1990 (11).

In our study coagulase-negative staphylococci were isolated in 25% of episodes of bacteremia. Bacteremia due to these organisms is frequently catheter-related (12). However, it has been demonstrated that coagulase-negative staphylococci can also arise from endogenous intestinal flora, especially in leukemic patients with severe neutropenia receiving an oral nonabsorbable antibiotic regimen lacking vancomycin (13). In our series the catheter was the source of coagulase-negative staphylococci bacteremia in 46% of the cases, whereas in 37% of the cases the origin was unknown.

In recent years viridans group streptococci have emerged as a major cause of bacteremia in neutropenic cancer patients, in particular among pa-

tients receiving high-dose chemotherapy with cytosine arabinoside, which produces severe oral mucositis, and prophylactic therapy with fluoroquinolone antibiotics (14, 15). At our hospital, where norfloxacin is used as a prophylactic agent, viridans group streptococci were the second most common organisms isolated from blood cultures, after coagulase-negative staphylococci. Chemotherapy-induced severe oral mucositis was considered the source of infection in approximately half of these cases. Significantly, we observed a dramatic increase in bacteremia due to viridans group streptococci over the study period.

This upward trend of viridans group streptococci bacteremia has also been observed in other institutions, such as the M.D. Anderson Cancer Center in Texas, where the incidence of viridans streptococci bacteremia rose from one case per 10,000 admissions in 1972 to 47 cases per 10,000 admissions in 1989 (15). Most viridans streptococcal infections have been associated with limited morbidity. However, bacteremia due to viridans group streptococci, especially *Streptococcus mitis*, can be accompanied by serious complications such as adult respiratory distress syndrome and shock (14, 15). In addition, the emergence of bacteremia due to penicillin-resistant strains, which has recently been reported, is also of major concern (16, 17). In our study *Streptococcus mitis* was the species most frequently isolated, and two patients with bacteremia due to highly penicillin-resistant strains developed respiratory distress and died.

Risk factors that have been associated with the increasing incidence of bacteremia caused by gram-positive organisms include the use of more intensive chemotherapy, which produces profound neutropenia and severe mucositis, the generalized use of central venous catheters, and the use of fluoroquinolone prophylaxis, which is effective against gram-negative bacteria (18–20). In the present study, in which approximately half of the patients had received prophylactic norfloxacin, we documented a significant increase in oral mucositis and catheter infection as sources of bacteremia. In our series the overall incidence of gram-negative bacteremia remained stable over time. However, at the end of 1990 we observed the emergence of fluoroquinolone-resistant strains of *Escherichia coli* causing bacteremia (21). This worrisome problem occurred in patients who had previously received prophylactic fluoroquinolones and has been also documented in other European institutions (22, 23).

In our study mortality seemed to decrease over the study period. However, the decrease is not statistically significant when the last year of the study is excluded from the analysis. These data can be confounding and must be analyzed with caution, because the figure of mortality reached in 1993 is probably an outlier.

In conclusion, we found a marked increase in gram-positive bacteremia, mainly caused by coagulase-negative staphylococci and viridans streptococci. This finding seems to be related to a significant increase in catheter infection and oral mucosa as sources of bacteremia, along with the extensive use of prophylactic fluoroquinolones. Although some approaches have been studied (24–26), better strategies to prevent chemotherapy-induced mucositis and catheter-related bacteremia are needed.

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